

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055873 A1

(51) International Patent Classification⁷: **C07D 317/48**,
319/16, C07C 211/38, A61K 31/357, 31/135, A61P 25/22,
25/24

(DK). **BREGNEDAL, Peter** [DK/DK]; Gærdesmuttevej
1B, DK-3450 Allerød (DK).

(21) International Application Number: PCT/DK02/00873

(22) International Filing Date:
18 December 2002 (18.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA200101939 21 December 2001 (21.12.2001) DK
60/343,360 21 December 2001 (21.12.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and

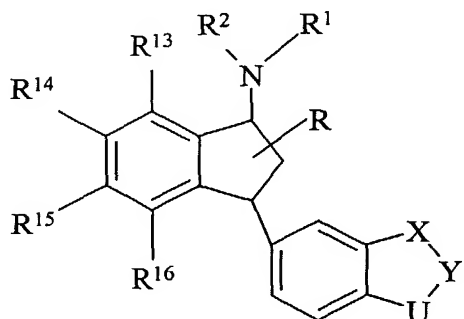
(75) Inventors/Applicants (*for US only*): **BØGESØ, Klaus, Peter** [DK/DK]; Hørsholm Park 16, 2.tv., DK-2970 Hørsholm (DK). **PÜSCHL, Ask** [DK/DK]; Holger Danskes Vej 20, 4 sal, DK-2000 Frederiksberg (DK). **KEHLER, Jan** [DK/DK]; Nymøllevej 28, DK-2800 Kgs. Lyngby

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMINOINDANE DERIVATIVES AS SEROTONIN AND NOREPINEPHRINE UPTAKE INHIBITORS



(I)

(57) Abstract: The present invention relates to aminoindane derivatives having the formula I wherein X, Y, U, R¹⁻², R¹³⁻¹⁶ and R are as defined in the claims, or an acid addition salt thereof. The compounds of the invention possess the combined effect of serotonin reuptake inhibition and norepinephrine uptake inhibition.

WO 03/055873 A1

Aminoindane derivatives as serotonin and norepinephrine uptake inhibitors

The invention provides novel aminoindane derivatives which are useful in the treatment of affective disorders, such as depression and anxiety disorders.

5

Background of the invention

The combined effect of serotonin reuptake inhibition and norepinephrine uptake inhibition on depression is explored in clinical studies of compounds such as Duloxetine (Wong DT : Duloxetine (LY-248686): an inhibitor of serotonin and noradrenaline uptake and an antidepressant drug candidate *Expert Opinion on Investigational Drugs* (1998) 7 10 1691-1699) and Venlafaxine (Khan-A; Fabre-LF; Rudolph-R: Venlafaxine in depressed outpatients *Psychopharmacology Bulletin* (1991) 27, 141-144).

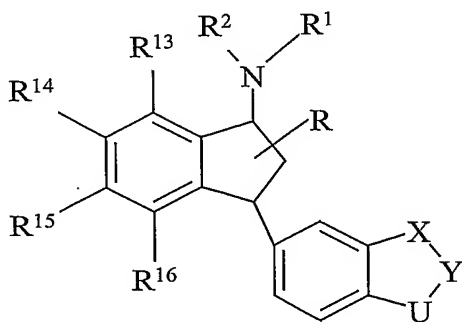
15

The present invention provides novel compounds which possess the combined effect of serotonin reuptake inhibition and norepinephrine uptake inhibition for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

20

Summary of the invention

25 The present invention relates to compounds having the formula I



I

wherein

X is -O-, -S- or $-\text{CR}^4\text{R}^5-$;

Y is $-\text{CR}^6\text{R}^7-$, $-\text{CR}^6\text{R}^7-\text{CR}^8\text{R}^9-$ or $-\text{CR}^6=\text{CR}^7-$; or X and Y together form a group -

5 $\text{CR}^4=\text{CR}^5-$, or $-\text{CR}^4=\text{CR}^5-\text{CR}^6\text{R}^7-$; and

U is -O-, -S- or $\text{CR}^{10}\text{R}^{11}$;

or

10 X is -O-, -S- or $-\text{CR}^4\text{R}^5-$; and

Y and U together form a group $\text{CR}^6=\text{CR}^7-$, $-\text{CR}^6=\text{CR}^7-\text{CR}^{10}\text{R}^{11}-$,

or $-\text{CR}^6\text{R}^7-\text{CR}^{10}=\text{CR}^{11}-$;

or X and Y and U together form $-\text{CR}^4=\text{CR}^5-\text{CR}^6=\text{CR}^7-$;

15

R^1 and R^2 are independently selected from hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-8} -cycloalkyl, or R^1 and R^2 together with the nitrogen, to which they are attached, form a 3-7-membered saturated ring optionally containing one further

20 heteroatom;

R^{13} , R^{14} , R^{15} and R^{16} are each independently selected from hydrogen, halogen, cyano, nitro, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, and C_{3-8} -cycloalkyl;

25 R is hydrogen, halogen, C_{1-6} -alkyl or cyano;

R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen and C_{1-4} -alkyl;

30 or an acid addition salt thereof;

The invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

- 5 The invention further provides the use of a compound of formula I or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression and anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific
10 phobias, social phobia and agoraphobia.

The invention also provides a method for the treatment of an affective disorder as mentioned above in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of formula I or a
15 pharmaceutically acceptable acid addition salt thereof.

Detailed description of the invention

According to one specific embodiment of the invention, X and U is selected from -O-
20 and -S- and Y is $-CR^6R^7-$ or $-CR^6R^7-CR^8R^9-$.

According to another specific embodiment of the invention, X and Y and U together form $-CR^4=CR^5-CR^6=CR^7-$.

- 25 Preferred compounds according to the invention are:
Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)diethylamine,
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)diethylamine,
30 Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)ethylamine,
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)ethylamine,
Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)methylamine,
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)methylamine,

- (+)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
 (-)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
 (+)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
 (-)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine,
 5 Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine,
 Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine,
 Cis-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine,
 Trans-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine,
 Cis-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine,
 10 Trans-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine,
 Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine,
 Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine,
 Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine,
 Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine,
 15 Cis-Enantiomer-1-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine and
 Cis-Enantiomer-2-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine or acid
 addition salts thereof.

As used herein halogen means fluoro, chloro, bromo or iodo.

20

The term C₁₋₆ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

- 25 Similarly, C₂₋₆ alkenyl and C₂₋₆ alkynyl, respectively, designate such groups having from two to six carbon atoms including one double bond and triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl

- 30 The term C₃₋₈ cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

R¹ and R² may together with the nitrogen atom to which they are attached form a 3-7 membered ring optionally containing one further heteroatom, such as aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

5 Exemplary of organic acid addition salts according to the invention are those formed with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic
10 acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of inorganic acid addition salts according to the invention are those formed with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. The acid addition salts of the invention are preferably pharmaceutically acceptable salts formed with non-toxic acids.

15

The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. The solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

20

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers or diastereomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

25

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Racemic compounds of the present invention can thus be resolved into their optical antipodes,
30 e.g., by fractional crystallisation of d- or l- (tartrates, mandelates or camphorsulphonate) salts for example. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix.

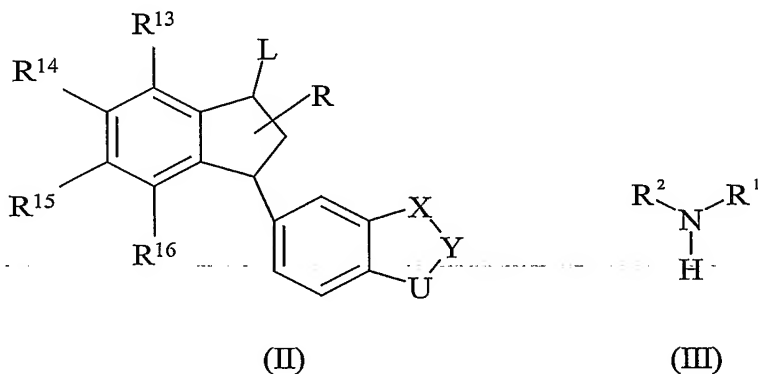
The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives or by enzymatic resolution.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

The compounds of the invention may be prepared by:

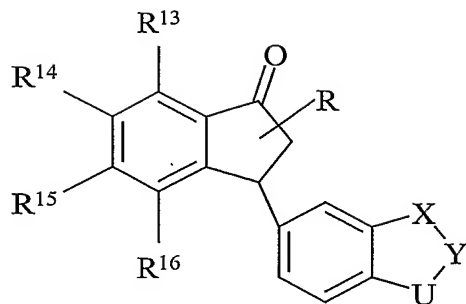
1) Alkylating an amine of formula III with an alkylating reagent of formula II:



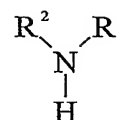
wherein R, R¹-R², R¹³⁻¹⁶, X, Y and U are as previously defined, and L is a leaving group such as halogen, mesylate or tosylate;

20

2) Reductive alkylation of an indane ketone of formula IV with an amine of formula III:



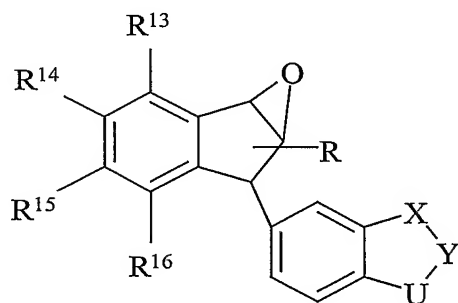
(IV)



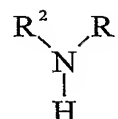
(III)

wherein R, R¹-R², R¹³⁻¹⁶, X, Y and U are as previously defined;

- 5 3) Opening an epoxide of formula V with an amine of formula III:



(V)



(III)

wherein R, R¹-R², R¹³⁻¹⁶, X, Y and U are as previously defined.

10

The alkylation according to method 1) is conveniently performed in an organic solvent such as an alcohol or ketone with a suitable boiling point, preferably in the presence of an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature, which is different from the boiling point, in one of the above-mentioned solvents or in dimethyl formamide (DMF), dimethylsulfoxide (DMSO) or N-methylpyrrolidin-2-one (NMP), preferably in the presence of a base such as those mentioned above. The alkylating derivatives of formula II have been described in the literature (e.g. Bøgesø, K.P. *J. Med. Chem.* **26**, 1983, 935-947; Bøgesø, K.P. *et al. J. Med. Chem.* **28**, 1985, 1817-1828; Sommer, M.B. *et al. J. Org. Chem.* **55**, 1990,

15

20

4822-4827 and references cited therein) and the amines of formula III are commercially available.

The reductive alkylation according to method 2) is performed by standard literature methods. The reaction can be performed in one step under standard reductive amination conditions using e.g. sodium cyanoborohydride or in two steps, e.g. by condensation of amines of formula III with a reagent of formula IV followed by reduction of the resulting imine with sodium cyanoborohydride or sodium borohydride. The ketones of formula IV can be prepared as described in the literature (e.g. Bøgesø, K.P. *J. Med. Chem.* **26**, 1983, 935-947; Bøgesø, K.P. *et al. J. Med. Chem.* **28**, 1985, 1817-1828; Sommer, M.B. *et al. J. Org. Chem.* **55**, 1990, 4822-4827 and references cited therein).

The epoxide opening according to method 3) is conveniently performed in an organic solvent such as a suitably boiling alcohol or ketone using an excess of an amine of formula III at reflux temperature.

Epoxides of formula IV can be prepared by methods described in the literature (e.g. Ghosh, A.K. *et al. Synthesis* **5**; 1997; 541-544; Palmer, M.J. *et al. J. Chem. Soc. Perkin Trans. 1*, 2002, 416 - 427).

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilising the solution and filling it in

suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

Experimental

The compounds of the invention exemplified in the following have been characterized using the following methods:

Melting points were determined on a Büchi B-540 apparatus and are uncorrected.

Mass spectra were obtained on a Quattro MS-MS system from VG Biotech, Fisons Instruments. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (50 X 4.6 mm YMC ODS-A with 5 μ m particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times R_t are expressed in minutes. Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 μ m particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (5:95:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^1H NMR spectra were recorded at 250.13 MHz on a Bruker AC 250 or at 500.13 MHz on a Bruker DRX 500. Deuterated chloroform (99.8% D) or dimethylsulfoxide

(99.9% D) were used as solvents. TMS was used as internal reference standard.

Chemical shifts are expressed as ppm values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qv=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of

5 triplets, m= multiplet, b=broad. NMR signals corresponding to acidic protons are to some extent omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. For column chromatography, silica gel of type Kieselgel 60, 40-60 mesh ASTM was used. For ion-exchange chromatography, the following material was used: SCX-columns (1 g) from Varian Mega Bond Elut®, Chrompack cat. No.
10 220776. Prior to use, the SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

15

Examples

Preparation of intermediates

20 A. Alkylating reagents

3-Amino-1-(benzo[1,3]dioxol-5-yl)-1-cyano-1H-indene-2-carboxylic acid methyl ester

A mixture of 2-chlorobenzonitrile (12.3 g) and benzo[1,3]dioxol-5-yl-acetonitrile (10 g) in dimethylformamide (25 mL) was added with stirring and cooling in an ice bath
25 to potassium *tert*-butoxide (20.1 g) dissolved in dimethylformamide (50 mL) at such a rate that the temperature did not exceed 25 °C. After stirring for 0.5 h, methyl chloroacetate (11.1 g) was added in 10 min. After being stirred for 24h at rt, the mixture was poured into a mixture of 0.1 M HCl (200 mL), heptane (30 mL) and toluene (15 mL). Stirring for 1 h, filtration and washing with water (2 x 50 mL),
30 toluene (2 x 10 mL) and heptane (2 x 25 mL) afforded 79% of 3-Amino-1-benzo[1,3]dioxol-5-yl-1-cyano-1H-indene-2-carboxylic acid methyl ester.

3-(Benzo[1,3]dioxol-5-yl)-indan-1-one

A mixture of 3-amino-1-benzo[1,3]dioxol-5-yl-1-cyano-1*H*-indene-2-carboxylic acid methyl ester (10 g) and acetic acid (30 mL) were heated to 100 °C; 60% aqueous sulfuric acid (20 mL) was added with stirring during 30 min. The mixture was heated
5 to 110 °C for 6 h, cooled to rt, extracted with toluene (50+10 mL), washed with water (3 x 100 mL), extracted with 0.1 M aqueous sodium hydroxide (100 + 20 mL), acidified with concentrated hydrochloric acid, extracted with toluene (25 + 10 mL), and filtrated through activated carbon. Removal of the toluene gave 80% of 1-(benzo[1,3]dioxol-5-yl)-3-oxo-indan-1-carboxylic acid. The acid was subsequently
10 decarboxylated by heating to 100 °C in N-methylpyrrolidone (15 mL) for 1 h. After cooling, the solution was poured into water (40 mL) with efficient stirring. Filtration, washing with water (5 x 20 mL), dissolution in ethyl acetate (40 mL), filtration through activated carbon and removal of the ethyl acetate gave 80% of 3-(benzo[1,3]dioxol-5-yl)-indan-1-one.

15

Cis-3-(benzo[1,3]dioxol-5-yl)-indan-1-ol

Sodium borohydride (1.5 g) was added in portions with stirring at 10-15 °C to a solution of 3-(benzo[1,3]dioxol-5-yl)-indan-1-one (10 g) in a mixture of ethanol (75
20 mL) and dimethoxyethane (75 mL). The mixture was stirred at rt for 1 h and then evaporated *in vacuo*. The resulting oil was treated with water and diethyl ether, and the organic phase was separated and washed with water and 0.1 N HCl, dried (MgSO₄) and evaporated *in vacuo* to give *cis*-3-(benzo[1,3]dioxol-5-yl)-indan-1-ol as a brown oil (10 g).

25

5-(3-Chloro-indan-1-yl)-benzo[1,3]dioxole

Thionyl chloride (7 mL) was added with stirring and cooling at 15 °C to a solution of *cis*-3-(benzo[1,3]dioxol-5-yl)-indan-1-ol (10 g) in dichloromethane (300 mL). The mixture was stirred at rt for 40 min. The mixture was washed twice with water, dried
30 (MgSO₄) and evaporated *in vacuo* to give a quantitative yield of 5-(3-chloroindan-1-yl)benzo[1,3]dioxole as an oil, which was used in the next step without further purification.

Preparation of the compounds of the invention**Example 1**

5 *trans*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (1) and *cis*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (2)

A mixture of 5-(3-chloroindan-1-yl)-benzo[1,3]dioxole (11 g) and 70 mL of 33% dimethylamine in ethanol was kept at 100 °C in a steel autoclave for 16h. The mixture was cooled and evaporated *in vacuo*. The residue was dissolved in diethylether and
10 washed with water and 2 N NaOH. The organic phase was dried (magnesium sulphate) evaporated *in vacuo* and the residue was purified by flash chromatography on silicagel using a gradient-eluent: 1) ethyl acetate/heptane (80:20) and 2) ethyl acetate/ethanol/triethylamine (90:10:4) to give the crude products as clear oils.

15 *Trans*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (1)

The slow-eluting compound is the *trans* isomer (3 g).

¹H NMR (CDCl₃): 1.95-2.05 (m, 1H); 2.30 (s, 6H); 2.60-2.70 (m, 1H); 4.40 (m, 2H); 5.90 (s, 2H); 6.55 (m, 1H); 6.65 (m, 1H), 6.70 (m, 1H), 6.95 (m, 1H), 7.25 (m, 1H), 7.45 (m, 1H). The compound could be converted to the fumarate salt from ethyl
20 acetate/ethanol as a white crystalline compound.

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (2)

The fast-eluting compound is the *cis* isomer (1 g).

¹H NMR (CDCl₃): 1.95-2.05 (m, 1H); 2.30 (s, 6H); 2.60-2.70 (m, 1H); 4.10 (m, 1H);
25 4.45 (m, 1H), 5.90 (s, 2H); 6.55 (m, 1H); 6.65 (m, 1H), 6.70 (m, 1H), 6.95 (m, 1H), 7.25 (m, 1H), 7.45 (m, 1H). The compound could be converted to the fumarate salt from ethyl acetate/ethanol as a white crystalline compound.

The following compounds 3-14 were prepared analogously, HPLC-retention time and
30 purity are described in table 1.:

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)diethylamine(3)

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)diethylamine(4)

- Trans*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)ethylamine (5)
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)ethylamine (6)
Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)methylamine (7)
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)methylamine (8)
5 *Trans*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine (13)
Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine (14)
Cis-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine (15)
Trans-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine (16)
Cis-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine (17)
10 *Trans*-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine (18)
Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine (19)
Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine (20)
Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine (21)
Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine (22)

15

Compound	Retention time (min)	Purity % (UV)	Purity % (ELSD)
1	1.88	85.18	99.12
2	1.9	93.92	99.26
3	1.83	99.25	99.72
4	1.87	95.85	99.69
5	1.58	100	95.80
6	1.73	86.91	99.74
7	1.79	94.36	99.59
8	1.86	95.34	99.70
13	1.83	78.3	98.1
14	1.89	81.8	93.3
15	1.73	78.1	99.8
16	1.68	84.7	92.7
17	2.10	92.5	99.8
18	2.10	92.8	99.9
19	2.08	75.1	97.7
20	1.89	96.4	99.7
21	2.08	81.8	96.3
22	2.00	86.8	97.1
23	1.83	82.4	99.1
24	1.87	77.3	98.5

Table 1

Example 2

5 (+)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (9) and (-)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (10)

Compound 1, trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine, was subjected to resolution by chiral HPLC using a Gilson SF3 supercritical fluid chromatography system equipped with chiralcelOD columns (4.6 mm x 25 cm for analytical and 10 mm x 25 cm for preparative runs). The particle size in the columns was 10 μ m. A solution of compound 1, trans-(3-benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine, (1 g) in methanol (1 mL) was injected in 40 μ L portions on a preparative column. The column was eluted with carbondioxide – modifier (75:25). The modifier was 2-propanol with diethylamine (0.5%) and trifluoroacetic acid (0.5%).
15 The flow was 18.9 mL/min at 20 Mpa. Fraction collection was triggered by UV-detection (210 nm). The fractions containing the separate products were pooled and evaporated *in vacuo* which gave the enantiomers 9 and 10.

20 (+)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (9): $\alpha = +14.0$ (conc. = 1% in Methanol)

(-)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (10): $\alpha = -14.7$ (conc. = 1% in Methanol)

Example 3

25

(+)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (11) and (-)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (12)

30 Compound 2, cis-(3-benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine, was subjected to resolution by chiral HPLC using a Gilson SF3 supercritical fluid chromatography system equipped with chiralcelOD columns (4.6 mm x 25 cm for analytical and 10 mm x 25 cm for preparative runs). The particle size in the columns was 10 μ m. A solution of compound 2, cis-(3-benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine, (1

g) in methanol (1 mL) was injected in 40 μ L portions on a preparative column. The column was eluted with carbondioxide – modifier (75:25). The modifier was 2-propanol with diethylamine (0.5%) and trifluoroacetic acid (0.5%). The flow was 18.9 mL/min at 20 Mpa. Fraction collection was triggered by UV-detection (210 nm). The fractions containing the separate products were pooled and evaporated *in vacuo* which gave the enantiomers **11** and **12**.

(+)-*cis*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (**11**): $\alpha = +3.3$ (conc. = 1% in Methanol)
10 **12.** (-)-*cis*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)dimethylamine (**12**): $\alpha = -4.4$ (conc. = 1% in Methanol)

The following compounds were prepared analogously:

(+)-*Cis*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine (**23**)
15 (-)-*Cis*-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine (**24**)

Pharmacological testing

The compounds of the invention were tested in well- recognised and reliable tests.
20 The tests were as follows:

Measurements of [3 H]noradrenaline uptake into rat cortical synaptosomes.

Fresh cortex from male Wistar rats (125-225 g) are homogenized in 0.32 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is homogenized (20 sec) in this assay buffer (6 mg original tissue/mL = 4 mg/well). Test compounds (or buffer) and 10 nM [3 H]-noradrenaline are added to deep 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM CaCl₂, 1.12 mM MgSO₄, 25 12.66 mM Na₂HPO₄, 2.97 mM NaH₂PO₄, 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% O₂/5% CO₂ for 10 min at 37 °C and pH is adjusted 7.4. The incubation is started by adding tissue to a final assay volume of 1 ml. 30 After 15 min incubation with radioligand at 37 °C, samples are filtered directly on

Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 1 mL assay buffer. Non-specific uptake is determined using talsupram (10 μ M final concentration). Duloxetine is included as reference in all experiments as dose-response curve.

5

Measurements of [3 H]-5-HT uptake into rat cortical synaptosomes.

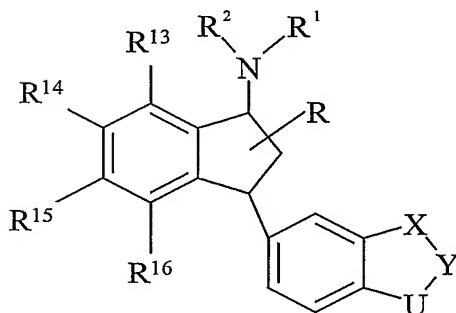
Whole brains from male Wistar rats (125-225 g), excluding cerebellum, are homogenized in 0.32 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is homogenized (20 sec) in this assay buffer (0.5 mg original tissue/well). Test compounds (or buffer) and 10 nM [3 H]-5-HT are added to 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM CaCl₂, 1.12 mM MgSO₄, 12.66 mM Na₂HPO₄, 2.97 mM NaH₂PO₄, 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% O₂/5% CO₂ for 10 min at 37 °C and pH is adjusted 7.4. The incubation is started by adding tissue to a final assay volume of 0.2 mL. After 15 min incubation with radioligand at 37 °C, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 0.2 ml assay buffer. Non-specific uptake is determined using citalopram (10 μ M final concentration). Citalopram is included as reference in all experiments as dose-response curve.

Results of the experiments showed that the compounds of the invention showed that the compounds all inhibit the norepinephrine and serotonin uptake with IC₅₀ below 200 nM.

30

Claims:

1. An aminoindane compound having the formula I



I

wherein

X is -O-, -S- or -CR⁴R⁵-;

Y is -CR⁶R⁷-, -CR⁶R⁷-CR⁸R⁹- or -CR⁶=CR⁷-; or X and Y together form a group -CR⁴=CR⁵-, or -CR⁴=CR⁵-CR⁶R⁷-, and

U is -O-, -S- or CR¹⁰R¹¹;

or

X is -O-, -S- or -CR⁴R⁵-; and

Y and U together form a group CR⁶=CR⁷-, -CR⁶=CR⁷-CR¹⁰R¹¹-, or -CR⁶R⁷-CR¹⁰=CR¹¹-;

or X and Y and U together form -CR⁴=CR⁵-CR⁶=CR⁷-;

R¹ and R² are independently selected from hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₈-cycloalkyl, or R¹ and R² together with the nitrogen, to which they are attached, form a 3-7 membered ring optionally containing one further heteroatom;

R^{13} , R^{14} , R^{15} and R^{16} are each independently selected from hydrogen, halogen, cyano, nitro, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, and C_{3-8} -cycloalkyl;

R is hydrogen, C_{1-6} -alkyl or cyano;

5

R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen and C_{1-4} -alkyl;

or an acid addition salt thereof.

10

2. A compound according to claim 1 wherein X and U is selected from -O- and -S- and Y is $-CR^6R^7-$ or $-CR^6R^7-CR^8R^9-$.

15

3. A compound according to claim 1 wherein X and Y and U together form $-CR^4=CR^5-CR^6=CR^7-$.

20

4. A compound according to claim 1 which is

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-diethyl-amine,

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-diethyl-amine,

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-amine,

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-amine,

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine,

25

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine,

(+)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

(-)-trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

(+)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

(-)-cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-dimethyl-amine,

30

Trans-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine,

Cis-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-ethyl-methyl-amine,

Cis-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine,

Trans-[3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-indan-1-yl]-dimethyl-amine,
Cis-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine,
Trans-Dimethyl-(3-naphthalen-2-yl-indan-1-yl)-amine,
Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine,
5 Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-dimethyl-amine,
Cis-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine,
Trans-[3-(6-Chloro-benzo[1,3]dioxol-5-yl)-indan-1-yl]-methyl-amine,
Cis-Enantiomer-1-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine and
Cis-Enantiomer-2-(3-Benzo[1,3]dioxol-5-yl-indan-1-yl)-methyl-amine
10 or an acid addition salt thereof.

5. A pharmaceutical composition comprising a compound according to claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

15

6. The use of a compound according to claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression and anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social
20 phobia and agoraphobia.

7. A method for the treatment of an affective disorder, including depression and anxiety disorders including general anxiety disorder, social anxiety disorder, post
25 traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound according to claims 1 to 4 or a pharmaceutically acceptable acid addition salt thereof.

30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 02/00873

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 317/48, C07D 319/16, C07C 211/38, A61K 31/357, A61K 31/135,
A61P 25/22, A61P 25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0271225 A2 (H. LUNDBECK A/S), 15 June 1988 (15.06.88), the claims, page 12, compounds 12, 18 --	1-4
X	WO 9518617 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD.), 13 July 1995 (13.07.95), the claims, page 27, line 15 - line 20, page 27, line 32 - line 37 --	1-7
X	WO 9935119 A1 (PHARM-ECO LABORATORIES, INC.), 15 July 1999 (15.07.99), page 1, page 8, fourth paragraph, page 12, first paragraph, the claims --	1-7

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 March 2003

Date of mailing of the international search report

25-03-2003

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Gerd Strandell/EÖ

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK. 02/00873

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9504028 A1 (SMITHKLINE BEECHAM PLC), 9 February 1995 (09.02.95), the claims, page 10, line 23 - line 25 --	1-7
X	WO 9504027 A1 (SMITHKLINE BEECHAM PLC), 9 February 1995 (09.02.95), the claims, page 10, line 16 - line 18 --	1-7
X	J. Med. Chem., Vol. 28, no. 12, 1985, Klaus P. Bogeso et al: "3-Phenyl-1-indanamines. Potential Antidepressant Activity and Potent Inhibition of Dopamine, Norepinephrine, and Serotonin Uptake", page 1817 - page 1828 --	1-7
X	WO 9322293 A1 (H. LUNDBECK A/S), 11 November 1993 (11.11.93) --	1-7
X	WO 9210192 A1 (H. LUNDBECK A/S), 25 June 1992 (25.06.92) --	1-7
X	WO 9855447 A1 (VENANTIUS LIMITED), 10 December 1998 (10.12.98), the claims -- -----	1-5

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/DK02/00873**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00873

Claim 7 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/12/02

International application No.

PCT/DK 02/00873

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	0271225	A2	15/06/88	SE	0271225 T3
				AT	95810 T
				AU	609751 B
				AU	8192887 A
				CA	1302420 A
				DE	3787790 D,T
				DK	626587 A
				ES	2059396 T
				FI	90660 B,C
				FI	875050 A
				GB	8628644 D
				IE	60380 B
				IE	873019 L
				IL	84429 A
				JP	2622135 B
				JP	63154652 A
				NO	175527 B,C
				NO	874990 A
				NZ	222614 A
				PT	86242 A,B
				US	4873344 A
				ZA	8708993 A
WO	9518617	A1	13/07/95	AU	1867095 A
				CA	2180841 A
				EP	0738149 A
				HU	75067 A
				HU	9601888 D
				IL	112292 A
				JP	9510188 T
				NO	962842 A
				US	5639913 A
				US	5877218 A
				US	5877221 A
				US	5880159 A
				US	5914349 A
				US	5994408 A
				US	6271263 B
				US	2002068839 A
				ZA	9500144 A
WO	9935119	A1	15/07/99	AU	752724 B
				AU	2027199 A
				CA	2317591 A
				EP	1044184 A
				JP	2002500211 T
				US	6268535 B
				US	6365894 B
				US	2001009267 A

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/12/02

International application No.

PCT/DK 02/00873

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9504028	A1	09/02/95	AU	7532094 A	28/02/95
				EP	0711272 A	15/05/96
				GB	9315566 D	00/00/00
				JP	9500879 T	28/01/97
				US	5773463 A	30/06/98
				ZA	9405504 A	26/01/96
WO	9504027	A1	09/02/95	AT	171934 T	15/10/98
				AU	7229394 A	28/02/95
				CA	2168257 A	09/02/95
				CN	1131414 A	18/09/96
				DE	69413827 D,T	29/04/99
				EP	0711271 A,B	15/05/96
				GB	9315600 D	00/00/00
				JP	9500880 T	28/01/97
				ZA	9405505 A	26/01/96
WO	9322293	A1	11/11/93	AT	194003 T	15/07/00
				AU	669709 B	20/06/96
				AU	4059993 A	29/11/93
				CZ	281676 B	11/12/96
				CZ	9402619 A	17/05/95
				DE	69328901 D,T	11/01/01
				DK	55192 D	00/00/00
				DK	638073 T	06/11/00
				EP	0638073 A,B	15/02/95
				SE	0638073 T3	
				ES	2148227 T	16/10/00
				FI	945042 A	26/10/94
				GR	3034396 T	29/12/00
				HK	1013816 A	00/00/00
				HU	71419 A	28/11/95
				HU	211909 B	29/01/96
				HU	9403098 D	00/00/00
				HU	9500587 A	30/10/95
				IL	105464 A	04/01/98
				JP	3255416 B	12/02/02
				JP	7505895 T	29/06/95
				KR	267635 B	01/11/00
				NO	306946 B	17/01/00
				NO	944090 A	20/12/94
				NZ	252098 A	28/05/96
				PT	638073 T	30/11/00
				RU	2114106 C	27/06/98
				SK	129394 A	10/05/95
				SK	281613 B	10/05/01
				US	5807855 A	15/09/98
				ZA	9302840 A	23/11/93

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/12/02

International application No.,

PCT/DK 02/00873

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9210192	A1	25/06/92	AT	121294 T	15/05/95
				AU	653375 B	29/09/94
				AU	8959991 A	08/07/92
				CA	2097715 A	05/06/92
				DE	69109132 D,T	31/08/95
				DK	286990 D	00/00/00
				DK	560868 T	02/10/95
				EP	0560868 A,B	22/09/93
				SE	0560868 T3	
				ES	2071479 T	16/06/95
				FI	105685 B	00/00/00
				FI	932541 A	23/07/93
				HK	122995 A	04/08/95
				IE	914076 A	17/06/92
				IL	100164 A	18/06/96
				JP	3245418 B	15/01/02
				JP	6503073 T	07/04/94
				NO	179947 B,C	07/10/96
				NO	932024 A	30/07/93
				NZ	240734 A	25/02/94
				PT	99673 A,B	30/10/92
				US	5643784 A	01/07/97
				ZA	9109563 A	26/08/92
WO	9855447	A1	10/12/98	AU	8031598 A	21/12/98
				IE	980421 A	05/05/99